

Application No. 09/780,650
Second Preliminary Amendment
Page 2

Table 1 provides a number of sample references which correlate the role of angiogenesis in numerous disease states.

Table 1

Disease State

Publication defining role of angiogenesis in disease state

atherosclerosis

PCT International Publication Number WO91/10424, Published July 25, 1991; Kahlon et al, *Angiogenesis in Atherosclerosis* Can. J. Cardio. (1992) (abstract)

Tumors

Moulton, K.S. Et al. *Angiogenesis in the huPBL-SCID Model of Human Transplant Rejection*. Transplantation Vol. 67 No. 12 Jun 1999 pp.1626-1631 (see page 1630, col. 2, lines 1-2 of the second paragraph); European Application Number 89100714.8, Published July 26, 1989.

solid tumors

PCT International Publication Number WO91/10424, Published July 25, 1991

benign tumors

Locci, M. Et al. *Angiogenesis: A New Diagnostic Aspect of Obstetric and Gynecologic Echography*. Journal of Perinatal Medicine Vol. 21 No. 6 1993 pp. 453-473 (page 469, abstract)

metastatic tumors

Mahadevan, V. Et al. *Metastasis and Angiogenesis*. Acta Oncologica Vol. 29 No. 1 1990 pp. 97-103 (page 97, abstract)

hemangiomas

PCT International Publication Number WO91/10424, Published July 25, 1991

nerve cell diseases

Siedlak, S.K. Et al. *Basic Fibroblast Growth Factor Binding Is a Marker for Extracellular Neurofibrillary Tangles in Alzheimer Disease*. The Journal of Histochemistry and Cytochemistry: Official Journal of the Histochemistry Society Vol. 37 No. 7 July 1991 pp. 899-904.

Application No. 09/780,650
Second Preliminary Amendment
Page 3

acoustic neuroma or
neurofibroma

Eldridge, R. *Central Neurofibromatosis with Bilateral Acoustic Neuroma*. Advances in Neurology Vol. 29 1981 pp. 57-65 (page 62-63, each paragraph)

diseases of the eye

See those listed for claim 65, as well as those on the copy of the attached chart filed for a related patent application 09/126,542 (copies of those references not attached)

retinopathy of prematurity

Penn, J.S. Et al. *Variable Oxygen Exposure Causes Preretinal Neovascularization in the Newborn Rat*. Investigative Ophthalmology & Visual Science Vol. 34 No. 3 Mar. 1993 pp. 576-585 (page 584, col. 2, final paragraph)

diabetic retinopathy

PCT International Publication Number WO91/10424, Published July 25, 1991

corneal graft rejection

Cursiefen, C. Et al. *Angiogenesis in Corneal Diseases: Histopathologic Evaluation of 254 Human Corneal Buttons with Neovascularization*. Cornea Vol. 17 No. 6 Nov. 1998 pp. 611-613

neovascular glaucoma

PCT International Publication Number WO91/10424, Published July 25, 1991

retrolental fibroplasias

PCT International Publication Number WO91/10424, Published July 25, 1991.

Trachoma

European Application Number 89100714.8, Published July 26, 1989

Degeneration

Penfold et al., *Age-related macular degeneration: ultrastructural studies of the relationship of leucocytes to angiogenesis*, Graefes Arch Clin Exp Ophthalmol 1987; 225(1):70-6 (abstract)

inflammation

Moulton, K.S. Et al. *Angiogenesis in the huPBL-SCID Model of Human Transplant Rejection*. Transplantation Vol. 67 No. 12 Jun 1999 pp. 1626-1631 (page 1626, col. 1, line 1)

Application No. 09/780,650
Second Preliminary Amendment
Page 4

pyogenic granulomas

Almeida, B.M. Et al. *The Distribution of LH39 Basement Membrane Epitope in the Tumour Stroma of Oral Squamous Cell Carcinomas*. The Journal of Pathology Vol. 166 No. 4 Apr. 1992 pp. 369-374 (page 369, last four lines of Summary); European Application Number 89100714.8, Published July 26, 1989

vascular malfunctions

Arnold, F. Et al. *Angiogenesis in Wound Healing*. Pharmacology & Therapeutics Vol. 52 No. 3 Dec. 1991 pp. 407-422; Poole, T.J. Et al. *Developmental Angiogenesis: Quail Embryonic Vasculature*. Scanning Microscopy Vol. 2 No. 1 Mar. 1998 pp. 443-448; European Application Number 89100714.8, Published July 26, 1989

abnormal wound healing

Arnold, F. Et al. *Angiogenesis in Wound Healing*. Pharmacology & Therapeutics Vol. 52 No. 3 Dec. 1991 pp. 407-422 (page 407, col. 2, line 1 of the second paragraph; page 412, section 2.4.5 "Negative Controls on Angiogenesis;" page 416, section 3.4 "Overhealing")

inflammatory disorders

Locci, M. Et al. *Angiogenesis: A New Diagnostic Aspect of Obstetric and Gynecologic Echography*. Journal of Perinatal Medicine Vol. 21 No. 6 1993 pp. 453-473 (page 453, second column, line 8)

Gout, gouty arthritis

three articles showing that factors inducing gout are IL-1, 2, and 6: Hashizume, K. Et al. *A Role of Interleukin-1 (IL-1) in Crystal-Induced Arthritis*. Advances in Experimental Medicine and Biology Vol. 253A 1989 pp. 219-224; Campen, D.H. Et al. *Serum Levels of Interleukin-2 Receptor and Activity of Rheumatic Diseases Characterized by Immune System Activation*. Arthritis and Rheumatism Vol. 31 No. 11 Nov. 1988 pp. 1358-1364; Brozik, M. Et. Al. *Interleukin 6 Levels in Synovial Fluids of Patients with Different Arthritides: Correlation with Local IgM Rheumatoid Factor and Systemic Acute Phase Protein Production*. The Journal of Rheumatology Vol. 19 No. 1 Jan. 1992 pp. 63-68; and five articles

Application No. 09/780,650
Second Preliminary Amendment
Page 5

showing that IL-1, 2, 4, 6 and 8 stimulate angiogenesis: Fan, T.P. Et al. *Stimulation of Angiogenesis by Substance P and Interleukin-1 in the Rat and its Inhibition by NK₁ or Interleukin-1 receptor antagonists*. British Journal of Pharmacology Vol. 110 No. 1 Sept. 1993 pp. 43-49; Cozzolino, F. Et al. *Interferon-alpha and Interleukin 2 Synergistically Enhance Basic Fibroblast Growth Factor Synthesis and induce Release, Promoting Endothelial Cell Growth*. The Journal of Clinical Investigation Vol.91 No. 6 Jun 1993 pp.2504-2512; Wojta, J. Et al. *Interleukin-4 Stimulates Expression of Urokinase-Type-Plasminogen Activator in Cultured Human Foreskin Microvascular Endothelial Cells*. Blood Vol. 81 No. 12 June 15, 1993 pp. 3285-3292; Sun, W.H. Et al. *In Vivo and in vitro Characteristics of Interleukin 6-transfected B16 Melanoma Cells*. Cancer Research Vol. 52 No. 19 Oct. 1, 1992 pp. 5412-5415; Hu, D.E. Et al. *Interleukin-8 Stimulates Angiogenesis in Rats*. Inflammation Vol. 17 No. 2 Apr. 1993 pp. 135-143

rheumatoid arthritis

PCT International Publication Number
WO91/10424, Published July 25, 1991

psoriasis

PCT International Publication Number
WO91/10424, Published July 25, 1991

immune disorders

PCT International Publication Number
WO91/10424, Published July 25, 1991

Behcet's Syndrome

Aydintug, A.O. et al. *Antibodies to Endothelial Cells in Patients with Behcet's Disease*. Clinical Immunology and Immunopathology Vol. 67 No. 2 May 1993 pp.157-162 (page 157, entire first col.; page 160, col. 2, second full paragraph)

Osler-Weber-Rendu disease

Burke et al., *Pulmonary arteriovenous malformation: a critical update*. Am. Rev. Respir. Dis. Vol 134(2) Aug 1986 334-9 (abstract); Van Cutsem et al., *Estrogen-progesterone treatment of Osler-Weber-Rendu disease*. J. Clin Gastroenterol Vol 10(6):676-9 Dec. 1988 (abstract)

Application No. 09/780,650
Second Preliminary Amendment
Page 6

~~Female Reproductive~~

~~system complications from
undesired angiogenesis~~

~~Locci, M. Et al. *Angiogenesis: A New Diagnostic Aspect of Obstetric and Gynecologic Echography*. Journal of Perinatal Medicine Vol. 21 No. 6 1993 pp. 453-473 (page 453, col. 1, line 25 to the end of col. 2); Logan, A. *Angiogenesis*. Lancet Vol. 341 No. 8858 Jun 1993 pp. 1467-1468 (page 1468, col. 1, first three full paragraphs)~~

~~Ovulation, implantation of a
blastula, menstruation,
menopause~~

~~Locci, M. Et al. *Angiogenesis: A New Diagnostic Aspect of Obstetric and Gynecologic Echography*. Journal of Perinatal Medicine Vol. 21 No. 6 1993 pp. 453-473 (page 453, col. 1, line 25 to the end of col. 2); Logan, A. *Angiogenesis*. Lancet Vol. 341 No. 8858 Jun 1993 pp. 1467-1468 (page 1468, col. 1, first three full paragraphs)~~

~~Osteoporosis~~

~~Schaub et al, *Novel agents that promote bone regeneration*, Curr Opin Biotechnol, 1991 Dec; 2(6):868-71 (abstract)~~

Please replace the third (3rd) paragraph on page 12, entitled Example 4, with the following paragraph:

Table 2 illustrates the inhibitory effects on tubulin polymerization *in vitro* exhibited by estradiol or estradiol derivatives, plant anti-mitotic compounds such as colchicine, combretastatin A-4 or other plant compounds. The method is given in Example 1.

Please replace the fourth (4th) paragraph on page 12, entitled Example 5, with the following paragraph:

Table 3 lists estrogens, estradiol or estradiol derivatives that inhibit colchicine binding to tubulin, by the method given in Example 3.